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HUYNH, PHUONG N

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/674,716	Applicant(s) BONNEFOY ET AL.	
	Examiner Phuong Huynh	Art Unit 1644	

-- Th MAILING DATE of this communication appears on the cover sh et with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *Three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11/6/00; 11/21/01; 7/8/02; 2/14/03* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-19* is/are pending in the application.

4a) Of the above claim(s) *15-17* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-14 and 18-19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *2* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. Claims 1-19 are pending.

2. Applicant's election with traverse of Group I, Claims 1-14 and 18-19 drawn to an antibody that binds to CD23, a pharmaceutical formulation comprising said antibody, filed 2/14/03, is acknowledged. The traversal is on the grounds that (1) the claims being so linked as to form a single general inventive concept under PCT Rule 13.1. (2) It would not constitute an undue burden to search and examine the claims of Group I and claims 15-17 in the same application. This is not found persuasive because of the reasons set forth in the restriction mailed 12/31/02. The inventions listed as Groups I-III do not relate to a single general inventive concept under PCT Rule 13.1 because, under unity of invention practice as it applies to cases filed under 35 U.S.C. 371, unity of invention between different categories of inventions will only be found to exist if specific combinations of inventions are present. Those combinations include:

A) A product and a special process of manufacture of said product.

B) A product and a process of use of said product.

C) A product, a special process of manufacture of said product and a process of use of said product.

D) A process and an apparatus specially designed to carry out said process.

E) A product, a special process of manufacture of said product, and an apparatus specially designed to carry out said process.

The allowed combinations do not include multiple products, multiple methods of using said products, and a method of making a product as claimed in the instant application, see MPEP§ 1850). Accordingly, Groups I-III are not so linked as to form a single general inventive concept and restriction is proper. Further, Groups I versus Groups II-III are drawn to distinct products such as antibody versus DNA. A prior art search also requires a literature search. It is a burden to search more than one invention. Therefore, the requirement of Group I and Groups II-III is still deemed proper and is therefore made FINAL.

3. Claims 15-17 are withdrawn from further consideration by the examiner, 37 C.F.R. 1.142(b) as being drawn to non-elected inventions.

4. Claims 1-14 and 18-19 are being acted upon in this Office Action.

5. The disclosure is objected to because of the following informalities: (1) "**heavy**" on page 19, line 21 should have been "**light**" in order to match with the sequence listing. (2) "**light**" on page 19 at line 24 should have been "**heavy**" in order to match with the sequence listing and the description on page 8 of the specification. Appropriate action is required.

6. Claim 7 is objected to because of typographical error, "them" should have been "the".

7. 35 U.S.C. 101 reads as follows:

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

8. Claims 12-14 are rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd.* v. *Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966). For examination purposes, "use" claims set forth in claims 12-14 are prosecuted as "methods of use".

9. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

10. Claims 1-14 and 18-19 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling only for:

(1) An antibody that binds specifically to the CD23 (FCεRII) type II molecule expressed on haematopoietic cells comprising light chain variable domains CDRL1, CDRL2, CDRL3, heavy chain variable domains CDRH1, CDRH2 and CDRH3 wherein CDRL1 consisting of the amino acid sequence RSSKSLLY KDGKTYLN of SEQ ID NO: 1, CDRL2 consisting of the amino acid sequence LMSTRAS of SEQ ID NO: 5, CDRL3 consisting of the amino acid sequence QQLVEYPFT of SEQ ID NO: 7, CDRH1 consisting of the amino acid sequence

GYWMS of SEQ ID NO: 9, CDRH2 consisting of the amino acid sequence EIRLKSDNYATHYAESVKG of SEQ ID NO: 11 and CDRH3 consisting of the amino acid sequence FID of SEQ ID NO: 13;

(2) A humanized antibody or chimeric antibody that binds specifically to the CD23 (FCεRII) type II molecule expressed on haematopoietic cells comprising light chain variable domains CDRL1, CDRL2, CDRL3, heavy chain variable domains CDRH1, CDRH2 and CDRH3 wherein CDRL1 consisting of the amino acid sequence RSSKSLLY KDGKTYLN of SEQ ID NO: 1, CDRL2 consisting of the amino acid sequence LMSTRAS of SEQ ID NO: 5, CDRL3 consisting of the amino acid sequence QQLVEYPFT of SEQ ID NO: 7, CDRH1 consisting of the amino acid sequence GYWMS of SEQ ID NO: 9, CDRH2 consisting of the amino acid sequence EIRLKSDNYATHYAESVKG of SEQ ID NO: 11 and CDRH3 consisting of the amino acid sequence FID of SEQ ID NO: 13;

(3) An antibody that binds specifically to the CD23 (FCεRII) type II molecule expressed on haematopoietic cells comprising light chain variable domains CDRL1, CDRL2, CDRL3, heavy chain variable domains CDRH1, CDRH2 and CDRH3 wherein CDRL1 consisting of the amino acid sequence RSSKSLLY KDGKTYLN of SEQ ID NO: 1, CDRL2 consisting of the amino acid sequence LMSTRAS of SEQ ID NO: 5, CDRL3 consisting of the amino acid sequence QQLVEYPFT of SEQ ID NO: 7, CDRH1 consisting of the amino acid sequence GYWMS of SEQ ID NO: 9, CDRH2 consisting of the amino acid sequence EIRLKSDNYATHYAESVKG of SEQ ID NO: 11, CDRH3 consisting of the amino acid sequence FID of SEQ ID NO: 13 and has an affinity constant equal to or greater than $1x10^{9}$ Ka Mo^{-1};

(4) A humanized antibody that binds specifically to the CD23 (FCεRII) type II molecule expressed on haematopoietic cells comprising light chain variable domains CDRL1, CDRL2, CDRL3, heavy chain variable domains CDRH1, CDRH2 and CDRH3 wherein CDRL1 consisting of the amino acid sequence RSSKSLLY KDGKTYLN of SEQ ID NO: 1, CDRL2 consisting of the amino acid sequence LMSTRAS of SEQ ID NO: 5, CDRL3 consisting of the amino acid sequence QQLVEYPFT of SEQ ID NO: 7, CDRH1 consisting of the amino acid sequence GYWMS of SEQ ID NO: 9, CDRH2 consisting of the amino acid sequence EIRLKSDNYATHYAESVKG of SEQ ID NO: 11, CDRH3 consisting of the amino acid sequence FID of SEQ ID NO: 13, and the human variable heavy chain framework amino acid

sequence retains the mouse heavy chain variable framework amino acids at positions 49, 66, 76, 77 and 94,

(5) A humanized antibody that binds specifically to the CD23 (FCεRII) type II molecule expressed on haematopoietic cells comprising light chain variable domains CDRL1, CDRL2, CDRL3, heavy chain variable domains CDRH1, CDRH2 and CDRH3 wherein CDRL1 consisting of the amino acid sequence RSSKSLLY KDGKTYLN of SEQ ID NO: 1, CDRL2 consisting of the amino acid sequence LMSTRAS of SEQ ID NO: 5, CDRL3 consisting of the amino acid sequence QQLVEYPFT of SEQ ID NO: 7, CDRH1 consisting of the amino acid sequence GYWMS of SEQ ID NO: 9, CDRH2 consisting of the amino acid sequence EIRLKSDNYATHYAESVKG of SEQ ID NO: 11, CDRH3 consisting of the amino acid sequence FID of SEQ ID NO: 13, and the human variable light chain framework amino acid sequence retains the mouse light chain variable framework amino acids at positions 64;

(6) A antibody comprising one or both of the amino acid sequences encoded by the nucleic acid sequence according to SEQ ID NO: 1 and 2;

(7) A antibody comprising one or both of the amino acid sequences encoded by the nucleic acid sequence according to SEQ ID NO: 17 and 17;

(8) An antibody that binds specifically to the CD23 (FCεRII) type II molecule expressed on haematopoietic cells comprising light chain variable domains CDRL1, CDRL2, CDRL3, heavy chain variable domains CDRH1, CDRH2 and CDRH3 wherein CDRL1 consisting of the amino acid sequence RSSKSLLY KDGKTYLN of SEQ ID NO: 1, CDRL2 consisting of the amino acid sequence LMSTRAS of SEQ ID NO: 5, CDRL3 consisting of the amino acid sequence QQLVEYPFT of SEQ ID NO: 7, CDRH1 consisting of the amino acid sequence GYWMS of SEQ ID NO: 9, CDRH2 consisting of the amino acid sequence EIRLKSDNYATHYAESVKG of SEQ ID NO: 11, CDRH3 consisting of the amino acid sequence FID of SEQ ID NO: 13 and a constant region consisting of an amino acid substitution at position from 248 to Ala and Gly to Ala at position of 250; and (9) A method of making any antibody mentioned above for screening for antibody which competitively inhibits the binding of any antibody mentioned above, **does not** reasonably provide enablement for:

(1) *any* antibody which "has sufficient" of the amino acid sequence of each CDR shown below such that the antibody is capable of binding to the CD23 (FCεRII) type II molecule expressed on haematopoietic cells: RSSKSLLY KDGKTYLN which is CDRL1 (SEQ ID NO: 3), LMSTRAS which is CDRL2 (SEQ ID NO: 5), QQLVEYPFT which is CDRL3 (SEQ ID NO: 7),

GYWMS which is CDRH1 (SEQ ID NO: 9), EIRLKSDNYATHYAESVKG which is CDRH2 (SEQ ID NO: 11) and "FID ...." which is CDRH3 (SEQ ID NO: 13);

(2) *any* antibody which binds to the CD23 (FCεRII) type II molecule expressed on haematopoietic cells or soluble CD23 characterized by an affinity constant equal to or greater than 1x109 Ka Mo^{-1};

(3) *any* antibody which competitively inhibits the binding of any antibody having the CDR sequence such as: RSSKSLLY KDGKTYLN which is CDRL1 (SEQ ID NO: 3), LMSTRAS which is CDRL2 (SEQ ID NO: 5), QQLVEYPFT which is CDRL3 (SEQ ID NO: 7), GYWMS which is CDRH1 (SEQ ID NO: 9), EIRLKSDNYATHYAESVKG which is CDRH2 (SEQ ID NO: 11) and "FID ...." which is CDRH3 (SEQ ID NO: 13), to the CD23 (FCεRII) type II molecule expressed on haematopoietic cells;

(4) *any* antibody which "has sufficient" of the amino acid sequence of each CDR shown below such that the antibody is capable of binding to the CD23 (FCεRII) type II molecule expressed on haematopoietic cells: RSSKSLLY KDGKTYLN which is CDRL1 (SEQ ID NO: 3), LMSTRAS which is CDRL2 (SEQ ID NO: 5), QQLVEYPFT which is CDRL3 (SEQ ID NO: 7), GYWMS which is CDRH1 (SEQ ID NO: 9), EIRLKSDNYATHYAESVKG which is CDRH2 (SEQ ID NO: 11) and FID ....which is CDRH3 (SEQ ID NO: 13) which is *any* "altered antibody";

(5) *any* antibody which "has sufficient" of the amino acid sequence of each CDR shown below such that the antibody is capable of binding to the CD23 (FCεRII) type II molecule expressed on haematopoietic cells: RSSKSLLY KDGKTYLN which is CDRL1 (SEQ ID NO: 3), LMSTRAS which is CDRL2 (SEQ ID NO: 5), QQLVEYPFT which is CDRL3 (SEQ ID NO: 7), GYWMS which is CDRH1 (SEQ ID NO: 9), EIRLKSDNYATHYAESVKG which is CDRH2 (SEQ ID NO: 11) and FID ....which is CDRH3 (SEQ ID NO: 13) which is *any* "altered antibody" wherein the altered antibody is *any* humanized antibody;

(6) *any* antibody which "has sufficient" of the amino acid sequence of each CDR shown below such that the antibody is capable of binding to the CD23 (FCεRII) type II molecule expressed on haematopoietic cells: RSSKSLLY KDGKTYLN which is CDRL1 (SEQ ID NO: 3), LMSTRAS which is CDRL2 (SEQ ID NO: 5), QQLVEYPFT which is CDRL3 (SEQ ID NO: 7), GYWMS which is CDRH1 (SEQ ID NO: 9), EIRLKSDNYATHYAESVKG which is CDRH2 (SEQ ID NO: 11) and FID ....which is CDRH3 (SEQ ID NO: 13) in which the framework of the

heavy chain includes the amino acid residues from *any* murine antibody at *any* of positions such as the ones recited in claim 6;

(7) *any* antibody which "has sufficient" of the amino acid sequence of each CDR shown below such that the antibody is capable of binding to the CD23 (FCεRII) type II molecule expressed on haematopoietic cells: RSSKSLLY KDGKTYLN which is CDRL1 (SEQ ID NO: 3), LMSTRAS which is CDRL2 (SEQ ID NO: 5), QQLVEYPFT which is CDRL3 (SEQ ID NO: 7), GYWMS which is CDRH1 (SEQ ID NO: 9), EIRLKSDNYATHYAESVKG which is CDRH2 (SEQ ID NO: 11) and FID ....which is CDRH3 (SEQ ID NO: 13) in which the framework of the light chain included any amino acid residues from *any* murine antibody at position 64;

(8) *any* pharmaceutical formulation comprising *any* antibody which "has sufficient" of the amino acid sequence of each CDR shown below such that the antibody is capable of binding to the CD23 (FCεRII) type II molecule expressed on haematopoietic cells: RSSKSLLY KDGKTYLN which is CDRL1 (SEQ ID NO: 3), LMSTRAS which is CDRL2 (SEQ ID NO: 5), QQLVEYPFT which is CDRL3 (SEQ ID NO: 7), GYWMS which is CDRH1 (SEQ ID NO: 9), EIRLKSDNYATHYAESVKG which is CDRH2 (SEQ ID NO: 11) and FID ....which is CDRH3 (SEQ ID NO: 13) and a pharmaceutically acceptable excipient, and

(9) *any* pharmaceutical formulation comprising *any* antibody which "has sufficient" of the amino acid sequence of each CDR shown below such that the antibody is capable of binding to the CD23 (FCεRII) type II molecule expressed on haematopoietic cells: RSSKSLLY KDGKTYLN which is CDRL1 (SEQ ID NO: 3), LMSTRAS which is CDRL2 (SEQ ID NO: 5), QQLVEYPFT which is CDRL3 (SEQ ID NO: 7), GYWMS which is CDRH1 (SEQ ID NO: 9), EIRLKSDNYATHYAESVKG which is CDRH2 (SEQ ID NO: 11) and "FID ...." which is CDRH3 (SEQ ID NO: 13) in combination with *any* immunomodulatory or *any* anti-inflammatory agent and a pharmaceutically acceptable excipient for treating *any* disease such as the ones recited in claim 12. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the lack of sufficient working examples, the unpredictability in the art and the amount of experimentation required to enable

one of skill in the art to practice the claimed invention. The specification disclosure is insufficient to enable one skilled in the art to practice the invention as broadly claimed without an undue amount of experimentation.

The specification discloses only one monoclonal antibody that binds to CD23 comprising SEQ ID NO: 2 and SEQ ID NO: 1. The specification further discloses a humanized CD23 antibody and a chimeric antibody that binds to the CD23 (FCεRII) type II molecule expressed on haematopoietic cells comprising light chain variable domains CDRL1, CDRL2, CDRL3, heavy chain variable domains CDRH1, CDRH2 and CDRH3 wherein CDRL1 consisting of the amino acid sequence RSSKSLLY KDGKTYLN of SEQ ID NO: 1, CDRL2 consisting of the amino acid sequence LMSTRAS of SEQ ID NO: 5, CDRL3 consisting of the amino acid sequence QQLVEYPFT of SEQ ID NO: 7, CDRH1 consisting of the amino acid sequence GYWMS of SEQ ID NO: 9, CDRH2 consisting of the amino acid sequence EIRLKSDNYATHYAESVKG of SEQ ID NO: 11 and CDRH3 consisting of the amino acid sequence FID of SEQ ID NO: 13. The specification further discloses that the said antibody has affinity constant (Ka) approximately 9 x 10^{10}/mol for screening for competitive inhibitor.

The specification does not teach how to make and use *any* antibody as set forth in claims 1-14 and 18-19 for treating any disease such as the ones recited in claim 12 because the term "has" is open-ended. It expands the amino acid sequence of each CDR such as the ones recited in claim 1 to include additional amino acid at either or both ends in addition to the ones that are already in claim 1. Further, the term "sufficient" is not defined in the specification as filed. The "..." follows the "FID" in claim 1 is ambiguous; it is not clear if there is additional undisclosed amino acids follows. There is insufficient guidance as to which amino acids could be added, deleted, substitute or which undisclosed amino acids follows "FID" and whether the undisclosed antibody would bind to CD23 on haematopoietic cells. Even if the antibody is limited to the amino acid sequence comprising light chain variable domains CDRL1 of SEQ ID NO: 3, CDRL2 of SEQ ID NO: 5, CDRL3 of SEQ ID NO: 7, and heavy chain variable domains CDRH1 of SEQ ID NO: 9, CDRH2 of SEQ IDN O: 11 and CDRH3 of SEQ ID NO: 13, there is no in vivo working example demonstrating that the antibody could treat any disorder such as the ones recited in claim 12, let alone any antibody having indefinite number of undisclosed amino acids, in turn, would be useful for treating any disorder such as rheumatoid arthritis. Since the antibody in claim 1 is not enabled, it follows that any antibody which competitively inhibits the binding of any undisclosed antibody set forth in claim 1 to the CD23 (Fcε RII) type II molecule expressed

on haematopoietic cells are not enabled. It follows that any antibody that binds to CD23 with a characteristic such as an affinity constant equal to or greater than $1x10^9$ Ka Mo^{-1} is not enabled.

With regard to claim 4, the term "altered" is vague at best. Given the alteration could be at the CDR regions of the heavy chain or light chain variable regions, there is insufficient guidance as to which amino acid residues within the CDR regions of the heavy chain or light chain variable regions of the antibody could be substitute, delete, or add and whether the resulting altered antibody would still bind to CD23 expressed on haematopoietic cells, in turn, would be useful for any purpose.

Abaza *et al* teach that even a single amino acid substitution outside the antigenic site can exert drastic effects on the reactivity of a protein with monoclonal antibody against the site (See abstract, in particular).

Ngo *et al* teach that the amino acid positions within the polypeptide/protein that can tolerate change such as conservative substitution or no substitution, addition or deletion which are critical to maintain the protein's structure/function will require guidance (see Ngo et al., 1994, The Protein Folding Problem and Tertiary Structure Prediction, pp. 492-495).

Kuby *et al* teach that antibody epitopes (B cell epitopes) are not linear and are comprised of complex three-dimensional array of scattered residues which will fold into specific conformation that contribute to binding (See Kuby 1994, page 94, in particular). Immunization with a peptide fragment derived from a full-length polypeptide may result in **antibody specificity** that differs from the antibody specificity directed against the native full-length polypeptide.

Without the specific amino acid residues and given the indefinite number of undisclosed antibody or "altered antibody" having unknown binding specificity, it is unpredictable which undisclosed antibody, such as "altered antibody", humanized antibody, chimeric antibody, antibody in which the heavy chain framework regions includes any amino acids residues from any murine antibody at any positions such as the ones recited in claim 6, or the light chain framework regions that included any amino acid from any murine antibody at position 64 or any antibody in which the constant region contains Ala at position 235 or 237 by the Kabat numbering system would bind specifically to CD23, in turn, would be effective for treating any disorder such as arthritis. Sine the amino acid sequence and the binding specificity of the undisclosed antibody as set forth in claim 1 is not enabled, it follows that the method of using said antibody for manufacturing a medicament for treating any disease or blocking soluble CD23 formation is not enabled. It also follows that any antibody in which the constant region contains

Ala at position 235 at position 235 and Ala at position 237 by the Kabat numbering system is not enabled. It also follows that any pharmaceutical formulation comprising any undisclosed antibody mentioned above or in combination with any immunomodulatory or any anti-inflammatory agent is not enabled.

With regard to claims 8 and 9, SEQ ID NO: 1, 2, 17 and 18 are nucleic acid sequences and not amino acid sequences as recited in claims 8-9. Even if the antibody is limited to the amino acid sequences encoded by the nucleic acid sequence selected from the group consisting of SEQ ID NO: 1, 2, 17 and 18, there is no in vivo working example demonstrating that the claimed antibody is effective for treating numerous disorder such as the ones recited in claim 12. A pharmaceutical formulation for treating any disorder such as autoimmune disease in the absence of in vivo data are unpredictable for the following reasons: (1) the antibody may be inactivated before producing an effect, i.e. such as proteolytic degradation, immunological inactivation or due to an inherently short half-life of the antibody; (2) other functional properties, known or unknown, may make the antibody unsuitable for in vivo therapeutic use, i.e. such as adverse side effects prohibitive to the use of such treatment. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992). Further, autoimmune diseases such as the ones recited in claim 12 can be species- and model-dependent, it is not clear that the reliance on in vitro binding assays accurately reflects the relative efficacy of using any undisclosed antibody for the claimed therapeutic strategy.

For these reasons, it would require undue experimentation of one skilled in the art to practice the claimed invention. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

In re wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), the decision of the court indicates that the more unpredictable the area is, the more specific enablement is necessary. In view of the quantity of experimentation necessary, the limited working examples, the unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of the claims, it would take an undue amount of experimentation for one skilled in the art to practice the claimed invention.

11. Claims 1-14 and 18-19 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

The specification does not reasonably provide a **written description** of (1) *any* antibody which "has sufficient" of the amino acid sequence of each CDR shown below such that the antibody is capable of binding to the CD23 (FCεRII) type II molecule expressed on haematopoietic cells: RSSKSLLY KDGKTYLN which is CDRL1 (SEQ ID NO: 3), LMSTRAS which is CDRL2 (SEQ ID NO: 5), QQLVEYPFT which is CDRL3 (SEQ ID NO: 7), GYWMS which is CDRH1 (SEQ ID NO: 9), EIRLKSDNYATHYAESVKG which is CDRH2 (SEQ ID NO: 11) and "FID ...." which is CDRH3 (SEQ ID NO: 13);

(2) *any* antibody which binds to the CD23 (FCεRII) type II molecule expressed on haematopoietic cells or soluble CD23 characterized by an affinity constant equal to or greater than 1x109 Ka Mo^{-1};

(3) *any* antibody which competitively inhibits the binding of any antibody having the CDR sequence such as: RSSKSLLY KDGKTYLN which is CDRL1 (SEQ ID NO: 3), LMSTRAS which is CDRL2 (SEQ ID NO: 5), QQLVEYPFT which is CDRL3 (SEQ ID NO: 7), GYWMS which is CDRH1 (SEQ ID NO: 9), EIRLKSDNYATHYAESVKG which is CDRH2 (SEQ ID NO: 11) and "FID ...." which is CDRH3 (SEQ ID NO: 13), to the CD23 (FCεRII) type II molecule expressed on haematopoietic cells;

(4) *any* antibody which "has sufficient" of the amino acid sequence of each CDR shown below such that the antibody is capable of binding to the CD23 (FCεRII) type II molecule expressed on haematopoietic cells: RSSKSLLY KDGKTYLN which is CDRL1 (SEQ ID NO: 3), LMSTRAS which is CDRL2 (SEQ ID NO: 5), QQLVEYPFT which is CDRL3 (SEQ ID NO: 7), GYWMS which is CDRH1 (SEQ ID NO: 9), EIRLKSDNYATHYAESVKG which is CDRH2 (SEQ ID NO: 11) and FID ....which is CDRH3 (SEQ ID NO: 13) which is *any* "altered antibody";

(5) *any* antibody which "has sufficient" of the amino acid sequence of each CDR shown below such that the antibody is capable of binding to the CD23 (FCεRII) type II molecule expressed on haematopoietic cells: RSSKSLLY KDGKTYLN which is CDRL1 (SEQ ID NO: 3), LMSTRAS which is CDRL2 (SEQ ID NO: 5), QQLVEYPFT which is CDRL3 (SEQ ID NO: 7), GYWMS which is CDRH1 (SEQ ID NO: 9), EIRLKSDNYATHYAESVKG which is CDRH2

(SEQ ID NO: 11) and FID ....which is CDRH3 (SEQ ID NO: 13) which is *any* "altered antibody" wherein the altered antibody is *any* humanized antibody;

(6) *any* antibody which "has sufficient" of the amino acid sequence of each CDR shown below such that the antibody is capable of binding to the CD23 (FCεRII) type II molecule expressed on haematopoietic cells: RSSKSLLY KDGKTYLN which is CDRL1 (SEQ ID NO: 3), LMSTRAS which is CDRL2 (SEQ ID NO: 5), QQLVEYPFT which is CDRL3 (SEQ ID NO: 7), GYWMS which is CDRH1 (SEQ ID NO: 9), EIRLKSDNYATHYAESVKG which is CDRH2 (SEQ ID NO: 11) and FID ....which is CDRH3 (SEQ ID NO: 13) in which the framework of the heavy chain includes the amino acid residues from *any* murine antibody at *any* of positions such as the ones recited in claim 6;

(7) *any* antibody which "has sufficient" of the amino acid sequence of each CDR shown below such that the antibody is capable of binding to the CD23 (FCεRII) type II molecule expressed on haematopoietic cells: RSSKSLLY KDGKTYLN which is CDRL1 (SEQ ID NO: 3), LMSTRAS which is CDRL2 (SEQ ID NO: 5), QQLVEYPFT which is CDRL3 (SEQ ID NO: 7), GYWMS which is CDRH1 (SEQ ID NO: 9), EIRLKSDNYATHYAESVKG which is CDRH2 (SEQ ID NO: 11) and FID ....which is CDRH3 (SEQ ID NO: 13) in which the framework of the light chain included any amino acid residues from *any* murine antibody at position 64;

(8) *any* pharmaceutical formulation comprising *any* antibody which "has sufficient" of the amino acid sequence of each CDR shown below such that the antibody is capable of binding to the CD23 (FCεRII) type II molecule expressed on haematopoietic cells: RSSKSLLY KDGKTYLN which is CDRL1 (SEQ ID NO: 3), LMSTRAS which is CDRL2 (SEQ ID NO: 5), QQLVEYPFT which is CDRL3 (SEQ ID NO: 7), GYWMS which is CDRH1 (SEQ ID NO: 9), EIRLKSDNYATHYAESVKG which is CDRH2 (SEQ ID NO: 11) and FID ....which is CDRH3 (SEQ ID NO: 13) and a pharmaceutically acceptable excipient, and

(9) *any* pharmaceutical formulation comprising *any* antibody which "has sufficient" of the amino acid sequence of each CDR shown below such that the antibody is capable of binding to the CD23 (FCεRII) type II molecule expressed on haematopoietic cells: RSSKSLLY KDGKTYLN which is CDRL1 (SEQ ID NO: 3), LMSTRAS which is CDRL2 (SEQ ID NO: 5), QQLVEYPFT which is CDRL3 (SEQ ID NO: 7), GYWMS which is CDRH1 (SEQ ID NO: 9), EIRLKSDNYATHYAESVKG which is CDRH2 (SEQ ID NO: 11) and "FID ...." which is CDRH3 (SEQ ID NO: 13) in combination with *any* immunomodulatory or *any* anti-inflammatory

agent and a pharmaceutically acceptable excipient for treating *any* disease such as the ones recited in claim 12.

The specification discloses only one monoclonal antibody that binds to CD23 comprising SEQ ID NO: 2 encoded by the polynucleotide of SEQ ID NO: 1. The specification further discloses a humanized CD23 antibody and a chimeric antibody that binds to the CD23 (FCεRII) type II molecule expressed on haematopoietic cells or soluble CD23 comprising light chain variable domains CDRL1, CDRL2, CDRL3, heavy chain variable domains CDRH1, CDRH2 and CDRH3 wherein CDRL1 consisting of the amino acid sequence RSSKSLLY KDGKTYLN of SEQ ID NO: 1, CDRL2 consisting of the amino acid sequence LMSTRAS of SEQ ID NO: 5, CDRL3 consisting of the amino acid sequence QQLVEYPFT of SEQ ID NO: 7, CDRH1 consisting of the amino acid sequence GYWMS of SEQ ID NO: 9, CDRH2 consisting of the amino acid sequence EIRLKSDNYATHYAESVKG of SEQ ID NO: 11 and CDRH3 consisting of the amino acid sequence FID of SEQ ID NO: 13. The specification further discloses that the said antibody has affinity constant (Ka) of $9 \times 10^{10}/mol^{-1}$ for screening assays.

With the exception of the specific antibody mentioned above, there is insufficient written description about the binding specificity and amino acid sequence of *any* antibody that "has sufficient" of the amino acid sequence of each CDR such as the ones recited in claim 1 because the term "has" is open-ended. It expands the amino acid sequence of each CDR such as the ones recited in claim 1 to include additional amino acid at either or both ends in addition to the ones that are already in claim 1. Further, the term "sufficient" is not defined in the specification as filed. The "..." follows the "FID" in claim 1 is ambiguous; it is not clear if there is additional undisclosed amino acids follows. There is insufficient written description about which amino acids could be added, deleted, substitute or which undisclosed amino acids follows "FID" and whether the undisclosed antibody would bind to CD23 on haematopoietic cells. With regard to claim 2, there is insufficient written description the antigenic determinant of any antibody that binds to the CD23 having a characteristic such as affinity constant equal to or greater than 1×10^9 Ka Mol^{-1}. Since the amino acid sequence of each CDR in claim 1 is insufficient described, any antibody which competitively inhibits the binding of said antibody, any humanized antibody, any chimeric antibody, any antibody in which the heavy chain framework regions includes any amino acids residues from any murine antibody at any positions such as the ones recited in claim 6, or the light chain framework regions that included any amino acid from any murine antibody at position 64 or any antibody in which the constant region contains Ala at position 235 or 237 by

the Kabat numbering system would bind specifically to CD23, in turn, would be effective for treating any disorder such as arthritis is not adequately described. Because the amino acid sequence and the binding specificity of the undisclosed antibody as set forth in claim 1 is not adequately described, it follows that the method of using said antibody for manufacturing a medicament for treating any disease or blocking soluble CD23 formation is not enabled. It also follows that any pharmaceutical formulation comprising any undisclosed antibody mentioned above or in combination with any immunomodulatory or any anti-inflammatory agent is not adequately described.

Further, the specification discloses only one monoclonal antibody, one humanized antibody and one chimeric antibody that binds to CD23 which is a type II molecule expressed on haematopoietic cells, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, Applicant was not in possession of the claimed genus. *See University of California v. Eli Lilly and Co. 43 USPQ2d 1398.*

Applicant is directed to the Revised Interim Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

12. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

13. Claim 1, 3-7, 8-14 and 18-19 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The recitation of "has sufficient" in claim 1 is indefinite and ambiguous because the specification does not define the term "sufficient". One of ordinary skill in the art cannot appraise the metes and bounds of the claimed invention.

The "amino acid sequences according to SEQ ID NOS: 1 and 2" in claim 8 is incorrect because SEQ ID NOS: 1 and 2 are nucleic acid sequences as disclosed in the sequence listing and **not** amino acid sequences as recited in said claims.

The "amino acid sequences according to SEQ ID NOS: 17 and 18" in claim 9 is incorrect because SEQ ID NOS: 17 and 18 are nucleic acid sequences as disclosed in the sequence listing

and **not** amino acid sequences as recited in said claims. One of ordinary skill in the art cannot appraise the metes and bounds of the claimed invention. Appropriate action is required.

Claim 12 provides for the use of an antibody in the manufacture of a medicament, but, since the claim does not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

Claim 13 provides for the use of an antibody which binds to CD23 (FCεRII) type II molecule expressed on haematopoietic cells in the manufacture of a medicament, but, since the claim does not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

Claim 14 provides for the use of an antibody but, since the claim does not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

14. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

15. The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

16. Claims 1, 2, 3, 6-7, and 11-14 are rejected under 35 U.S.C. 102(b) as being anticipated by Bonnefoy *et al* (J Immunology 138: 2970-78, May 1987, PTO 1449).

Bonnefoy *et al* teach an antibody such as monoclonal antibody Mab 9P25 that binds to the CD23 (FCεRII) type II molecule expressed on haematopoietic cells such as human lymphoid cells such as B cells (See Table III, page 2973, in particular) having an affinity constant Ka of 10 M^{-1} which is greater than the claimed affinity constant of 9 M^{-1} (See page 2973, column 2, first paragraph, in particular). Bonnefoy *et al* teach a method of manufacturing the reference monoclonal antibody (See page 2972, column 1, Production of a Mab inhibiting the binding of IgE to lymphoid FCεRL, in particular). The reference antibody Mab 25 inherently blocks soluble CD23 formation. The reference antibody 9P25 appears to has sufficient of the amino acid sequence of each CDR as set forth in claim 1 such that that reference antibody is capable of binding to the CD23 (FCεRII) type II molecule expressed human lymphoid cells such as B cells. The term "has" in claim 1 is open-ended. It expands the amino acid sequence of each CDR to include additional amino acids at either or both ends. Further, the term "sufficient" is indefinite, and so long the reference antibody is capable of binding to the CD23 expressed CD23 (FCεRII) type II molecule expressed on haematopoietic cells, the reference antibody appears to meet the claimed limitation since "sufficient" could be as little as one amino acid in each CDR. Since the Patent Office does not have the facilities for examining and comparing the antibodies of the instant invention to those of the prior art, the burden is on applicant to show that the prior art antibody is different from the claimed antibody. See In re Best, 562 F.2d 1252, 195 USPQ 430(CCPA 1977). Claims 6 and 7 are included in this rejection because the reference antibody is a mouse (murine) antibody that inherently includes the amino acid residues in the framework of heavy and light chains of the murine antibody. Claims 11-14 are included in this rejection because a product is a product, irrespective of how it is being used. Thus, the reference teachings anticipate the claimed invention.

17. Claims 2, 11 and 13 are rejected under 35 U.S.C. 102(b) as being anticipated by EP 0788,513 (Feb 1996, PTO 892).

The '413 European patent teaches an antibody such as B3B4 that binds to the CD23 (FCεRII) type II molecule which is a surface IgE low affinity receptor expressed on haematopoietic cells such as B cells (See page 3, lines 37- 43, page 9, Table 2, in particular). The reference anti-CD23 antibody inherently binds with an affinity constant equal to or greater than

1x 10^9 Mo^{-1} (1 nM) since the reference antibody is used for treatment of arthritis (See pages 7-8, Example 1, in particular). The '413 patent further teaches the use of the reference antibody in manufacture of a medicament to improve clinical severity of rheumatoid arthritis (See page 8, in particular) and the reference anti-CD23 antibody inherently blocks soluble CD23 formation associated said rheumatoid arthritis. Thus, the reference teachings anticipate the claimed invention.

18. Claims 1, 2, 3, 6-7, and 11-14 are rejected under 35 U.S.C. 102(b) as being anticipated by Plater-Zyberk *et al* (Nature Medicine 1(8): 781-785, May 1995, PTO 1449).

Plater-Zyberk *et al* teach an antibody such as monoclonal antibody Mab 25 that binds to the CD23 (FCεRII) type II molecule expressed on haematopoietic cells such as B cells with an inherent affinity constant equal to or greater than 1x 10^9 Mo^{-1} (1 nM) since the reference antibody is used for treatment of arthritis that inherently blocks soluble CD23 formation (See entire document, page 782 Table 1, in particular). The reference antibody Mab 25 inherently blocks soluble CD23 formation. Plater-Zyberk *et al* teach the use of the reference antibody for inhibiting the clinical and histological progression of established arthritis (see page 784, column 1, in particular). The reference antibody Mab 25 inherently blocks soluble CD23 formation. The reference antibody 9P25 appears to has sufficient of the amino acid sequence of each CDR as set forth in claim 1 such that that reference antibody is capable of binding to the CD23 (FCεRII) type II molecule expressed human lymphoid cells such as B cells. The term "has" in claim 1 is open-ended. It expands the amino acid sequence of each CDR to include additional amino acids at either or both ends. Further, the term "sufficient" is indefinite, and so long the reference antibody is capable of binding to the CD23 expressed CD23 (FCεRII) type II molecule expressed on haematopoietic cells, the reference antibody appears to meet the claimed limitation since "sufficient" could be as little as one amino acid in each CDR. Since the Patent Office does not have the facilities for examining and comparing the antibodies of the instant invention to those of the prior art, the burden is on applicant to show that the prior art antibody is different from the claimed antibody. See In re Best, 562 F.2d 1252, 195 USPQ 430(CCPA 1977). Claims 6 and 7 are included in this rejection because the reference antibody is a mouse (murine) antibody, which inherently includes the amino acid residues in the framework of heavy and light chains of the murine antibody. Claims 11-14 are included in this rejection because a product is a product,

irrespective of how it is being used. Thus, the reference teachings anticipate the claimed invention.

19. Claims 2, 11 and 13 are rejected under 35 U.S.C. 102(e) as being anticipated by US Pat No 6,011,138 (Jan 2000, PTO 892).

The '138 patent teaches various antibodies such as 1H6, 2C8, 5E8 and 6G5 which are anti-human CD23 monoclonal antibodies that bind to the CD23 (FCεRII) type II molecule expressed on haematopoietic cells such as B cells having an affinity constant Ka ranging from 0.01 nM to 1000 nM which is equal to or greater than $1x\ 10^9\ Mo^{-1}$ (1 nM) (See claims 1-8, in particular). The '138 patent teaches a method of making the reference CD23 monoclonal antibodies for use in human therapy such as treating allergic conditions, autoimmune diseases and inflammatory disease in human (See column 9, line 1, column 39, lines 55-58, in particular). The reference antibodies inherently blocks soluble CD23 formation when they bind to the CD23 (FCεRII) type II molecule expressed on haematopoietic cells. Thus, the reference teachings anticipate the claimed invention.

20. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 103(a) that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

21. This application currently names joint inventors. In considering Patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

22. Claims 1, 4-5, 11 and 18-19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bonnefoy *et al* (J Immunology 138: 2970-78, May 1987, PTO 1449) or Plater-Zyberk *et al* (Nature Medicine 1(8): 781-785, May 1995, PTO 1449) each in view of US Pat No. 5,658,570 (of record, Aug 1997, PTO 892).

The teachings of Bonnefoy *et al* and Plater-Zyberk *et al* have been discussed supra.

The claimed invention as recited in claim 4 differs from the teachings of the references only that the antibody is an altered antibody.

The claimed invention as recited in claim 5 differs from the teachings of the references only that the antibody is a humanized antibody.

The '570 patent teaches an altered antibody such as chimeric or humanized anti-CD23 antibodies which comprise a human constant region of IgG isotype and a primate antigen binding region to minimize immunogenicity of antibodies for therapy (See claims 1-8, and column 8, lines 52-53) and a method of administering a therapeutically amount of said antibodies (See column 6, lines 1-8, in particular). The '570 patent teaches a pharmaceutical composition comprising the reference chimeric humanized antibodies and a pharmaceutically acceptable excipient such as 0.4% saline (See column 22, lines 116, column 25, lines 20-30, claim 29 of '570 patent, in particular). The '570 patent teaches that humanized antibodies ensure that they appear more human-like so that the probability of adverse reaction is lessened (See column 5, lines 32-38, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the Mab 25 as taught by Plater-Zyberk *et al* to minimize immunogenicity of any antibody as taught by the '570 patent for therapy of chronic disease. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because the '570 patent teaches that humanized antibodies ensure that they appear more human-like so that the probability of adverse reaction is lessened and thereby minimize immunogenicity of any antibody for therapy of chronic disease (See column 5, lines 32-38, in particular).

23. Claims 8-9 and 10 are free of prior art.

24. No claim is allowed.

25. Any inquiry concerning this communication or earlier communications from the examiner should be directed to "Neon" Phuong Huynh whose telephone number is (703) 308-4844. The examiner can normally be reached Monday through Friday from 9:00 am to 6:00 p.m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

26. Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform to the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-7401.

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